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Attorney Docket 248432800200

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COMMISSIONER FOR PATENTS

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Patents and Trademarks, Washington, D.C. 20231.



Paola Quinonez  
Typed or Printed Name of Person Mailing Paper or Fee)  
(Signature of Person Mailing Paper or Fee)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 4,844,882

Issued: July 4, 1989

To: Widder et al.

For: CONCENTRATED STABILIZED  
MICROBUBBLE-TYPE ULTRASONIC  
IMAGING AGENT

TRANSMITTAL LETTER

The Honorable Commissioner of Patents  
and Trademarks  
Box Patent Extension  
Washington, D.C. 20231

Sir:

Enclosed are the following:

1. Application for Extension of Patent Term Under 35 U.S.C. Section 156.
2. A Certified Duplicate Application for Extension of Patent Term Under  
35 U.S.C. Section 156.
3. Three (3) Working Copies of Application for Extension of Patent Term Under  
35 U.S.C. Section 156.
4. A check in the amount of \$1,000.00.

In the unlikely event that the transmittal letter is separated from this document and the  
Patent Office determines that an extension and/or other relief is required, applicants petition for any

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required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to our Deposit Account No. 03-1952.

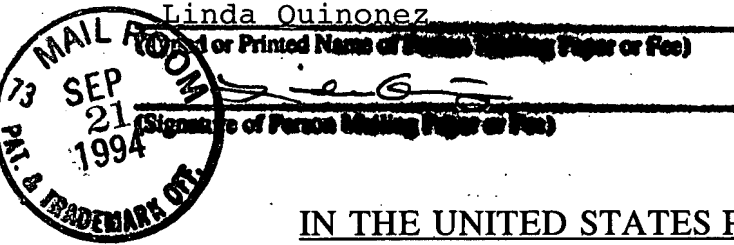
Respectfully submitted,

By Freddie K. Park  
Freddie K. Park  
Registration No. 35,636

Date: September 21, 1994

MORRISON & FOERSTER  
755 Page Mill Road  
Palo Alto, CA 94304-1018  
(415) 813-5600  
Fax: (415) 494-0792

Be available Copy  
CERTIFICATE OF MAILING BY **EXPRESS MAIL**  
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Date of Deposit **September 21, 1994**  
I hereby certify that this paper or film is being deposited  
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indicated above and is submitted to the Commissioner of  
Patents and Trademarks, Washington, D.C. 20231.



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 4,844,882

Issued: July 4, 1989

To: Widder et al.

For: CONCENTRATED STABILIZED  
MICROBUBBLE-TYPE ULTRASONIC  
IMAGING AGENT

APPLICATION FOR EXTENSION OF PATENT  
TERM UNDER 35 U.S.C. SECTION 156

The Honorable Commissioner of Patents  
and Trademarks  
Box Patent Extension  
Washington, D.C. 20231

Sir:

In accordance with the provisions of 35 U.S.C. section 156, Molecular Biosystems, Inc., a corporation of the state of Delaware, having a place of business at 10030 Barnes Canyon Road, San Diego, California, 92121-2729 (hereinafter referred to as "MBI") represent that they are the assignee of the entire interest in and to Letters Patent of the United States No. 4,844,882 granted to Kenneth J. Widder and Peter J. Westkaemper for CONCENTRATED STABILIZED MICROBUBBLE-TYPE ULTRASONIC IMAGING AGENT by virtue of an assignment in favor of MBI, recorded on January 21, 1988, Reel 4834, Frames 803. See Appendix Tab A for a copy of the assignment. This application is submitted by Applicant's authorized agent as set forth in 37 C.F.R. section 1.730. See Appendix Tab B for a copy of the Power of Attorney authorizing the undersigned to act in this manner. Applicant hereby submits this application for extension of patent term under 35 U.S.C. section 156 by providing the following information as set forth in 37 C.F.R. section 1.740.

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COMMISSIONER FOR PATENTS

(1) The approved product is identified as ALBUNEX® which is used for ultrasonic imaging in medical procedures. ALBUNEX® comprises a suspension of albumin microspheres which is produced by sonication of a 5% solution of human albumin.

(2) The approved product was subject to regulatory review under Section 515 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(e)).

(3) The approved product received permission for commercial marketing and use under Section 515 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360(e)) on August 5, 1994.

(4) This Application of extension of the patent term under 35 U.S.C. section 156 is being submitted within the statutory 60 day period, said period will expire on October 4, 1994.

(5) The complete identification of the patent for which extension is being sought is as follows:

Inventors: Kenneth J. Widder and Peter J. Westkaemper

Patent Number: 4,844,882

Issue Date: July 4, 1989

Expires: July 4, 2006

(6) See Appendix Tab C for a copy of the patent identified in Paragraph (5) hereof.

(7) A receipt of maintenance fee payment has been issued with regard to U.S. Patent No. 4,844,882. A copy of the maintenance fee receipt is attached as Appendix Tab D. No disclaimer, reexamination certificate or Certificate of Correction have been issued in connection with U.S. Patent No. 4,844,882.

STATEMENT PURSUANT TO 37 CFR 1.740(a)(9)

(8) U.S. Patent 4,844,882 claims the approved product. Claims 1-8 describe a microbubble-type imaging agent which is the approved product. The manner in which each applicable patent claim reads on the approved products is as follows:

Claim 1 of U.S. Patent No. 4,844,882 claims a concentrated, storable ultrasonic imaging agent, comprising an aqueous parenteral medium containing a dispersion of microspheres predominantly of diameters less than 10 microns, said microspheres consisting of gas microbubbles enclosed by solid walls formed from heat-insolubilized biocompatible material, said imaging agent having a homogeneously dispersed concentration of greater than  $1 \times 10^8$  microspheres per milliliter for over 4 weeks at a temperature of 20° to 25°C.

ALBUNEX® consists of microspheres that have diameters from 1 to 9 microns. These microspheres consist of gas microbubbles enclosed by solid walls formed from heat-insolubilized human serum albumin, a biocompatible protein. ALBUNEX® has a homogeneously dispersed concentration of 3 to  $5 \times 10^8$  microspheres per milliliter. The concentration of microspheres in said medium is greater than  $1 \times 10^8$  microspheres per milliliter for over 4 weeks at a temperature of 20 to 25 °C. Therefore, claim 1 embraces the product ALBUNEX®.

Claim 2 of U.S. Patent No. 4,844,882 claims an imaging agent of claim 1 in which said biocompatible material is a heat sensitive protein.

ALBUNEX® contains human serum albumin. Human serum albumin is a heat sensitive protein. Therefore, claim 2 embraces the product ALBUNEX®.

Claim 3 of U.S. Patent No. 4,844,882 claims an imaging agent of claims 1 and 2 in which at least 80% of said microspheres have diameters in the range from 1 to 9 microns.

Microspheres having diameters in the range from 1 to 9 microns are suitable for intravenous administration. Human serum albumin produces microspheres having a diameter in the range from 1 to 9 microns. Therefore, claim 3 embraces the product ALBUNEX®.

Claim 4 of U.S. Patent No. 4,844,882 claims an imaging agent of claim 1 in which said biocompatible material is human serum albumin.

ALBUNEX® consists of human serum albumin. Human serum albumin is available commercially as a sterile 5% aqueous solution, which can be used directly as the starting material for preparing the microspheres. Thus, claim 4 embraces the product ALBUNEX®.

Claim 5 of U.S. Patent No. 4,844,882 claims imaging agents of claims 1 or 4 in which said gas is air.

ALBUNEX® contains microspheres which consist of gas microbubbles encapsulated in human serum albumin. When the sonication is carried out in contact with air as the ambient atmosphere, the microspheres have air centers. Air is believed to be the most convenient ambient atmosphere. Therefore, claim 5 embraces the product ALBUNEX®.

Claim 6 of U.S. Patent No. 4,844,882 claims a concentrated, storable ultrasonic imaging agent comprising an aqueous parenteral medium containing a dispersion of microspheres at least 80% of which have diameters in the range of 1 to 9 microns, said microspheres consisting of gas microbubbles enclosed by solid walls formed from heat-insolubilized protein, said imaging agent having a homogeneously dispersed concentration of greater than  $1 \times 10^8$  microspheres per milliliter, said microspheres being stabilized in said medium as evidenced by maintaining a concentration of greater than  $1 \times 10^8$  microspheres per milliliter for over 4 weeks at a temperature of 20° to 25°C.

ALBUNEX® consists of microspheres that have diameters from 1 to 9 microns. These microspheres consist of gas microbubbles enclosed by solid walls formed from human serum albumin, a heat-insolubilized protein. ALBUNEX® has a homogeneously dispersed concentration of 3 to 5 X  $10^8$  microspheres per milliliter. The concentration of microspheres in said medium is greater than  $1 \times 10^8$  microspheres per milliliter for over 4 weeks at a temperature of 20 to 25°C. Therefore, claim 6 embraces the product ALBUNEX®.

Claim 7 of U.S. Patent No. 4,844,882 claims an imaging agent of claim 6 in which said protein is human serum albumin and said gas is air.

ALBUNEX® contains microspheres that consist of gas microbubbles encapsulated by human serum albumin. When the sonication is carried out in contact with air as the ambient atmosphere, the microspheres have air centers. Air is believed to be the most convenient ambient atmosphere. Therefore, claim 7 embraces the product ALBUNEX®.

Claim 8 of U.S. Patent No. 4,844,882 claims an imaging agent of claims 6 or 7 in which said medium is an aqueous solution of the protein of the microsphere walls. The walls of the microspheres contained in ALBUNEX® are formed from human serum albumin. Claim 8 describes an imaging agent that has a medium that is an aqueous solution of the protein of the microspheres. The human serum albumin is a solution protein of the microsphere. Therefore, claim 8 embraces the product ALBUNEX®.

STATEMENT PURSUANT TO 37 CFR 1.740(a)(10)

(9) The relevant dates and information, pursuant to 35 USC §156(g), to enable the Secretary of Health and Human Services to determine the applicable regulatory review period are as follows:

(i) As shown in "Appendix E," the Investigational Device Exemption for Alunex™ was filed on August 18, 1987.

(ii) The application for product approval was submitted September 11, 1990.

(iii) The application was approved by the Food and Drug Administration August 5, 1994.

STATEMENT PURSUANT TO 37 CFR §1.740(a)(11)

(9) As a brief description of the activities undertaken by the marketing applicant, MBI, during the applicable regulatory review period as set forth in 37 CFR §1.704(a)(11), attached hereto as "Appendix E" is a chronology of the major communications between MBI and the FDA from about August 18, 1987 until about August 5, 1994.



STATEMENT PURSUANT TO 37 CFR §1.740(a)(12)

(10) Applicant is of the opinion that U.S. Patent No. 4,844,882 is eligible for extension under 35 U.S.C. section 156 because it satisfies all the requirements for such extensions as follows:

(a) 35 U.S.C. section 156(a)

U.S. Patent No. 4,844,882 claims a method of ultrasonic imaging using the approved product, ALBUNEX®.

(b) 35 U.S.C. section 156(a)(1)

The term of U.S. Patent No. 4,844,882 has not expired before submission of this application.

(c) 35 U.S.C. section 156(a)(2)

The term of U.S. Patent No. 4,844,882 has never been extended.

(d) 35 U.S.C. section 156(a)(3)

The application for extension is submitted by MBI, an assignee of the entire interest of U.S. Patent No. 4,844,882. See Appendix Tab A.

(e) 35 U.S.C. section 156(a)(4)

The product, ALBUNEX®, has been subject to a regulatory review period before its commercial marketing or use.

(f) 35 U.S.C. section 156(a)(5)(a)

The commercial marketing or use of the product, ALBUNEX®, after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. section 355) under which such regulatory period occurred.

(11) The length of extension of the patent term of U.S. Patent No. 4,844,882, claimed by MBI is 2.09 years or 763 days. The length of the extension was determined as follows:

(a) The regulatory review period under 35 U.S.C. section 156(g)(3)(A) as set forth in 37 CFR §1.777(c)(1), the testing period, which began August 18, 1987, with the filing of the IDE and ended with the submission of the request for product approval on September 11, 1990 which is 3.07 years or 1121 days, and in §1.777(c)(2), the approval period, which began September 11, 1990, with the submission of the request for product approval and ended August 5, 1994 with the approval of the product which is 3.90 years or 1425 days and is a total of 6.72 years or 2545 days.

(i) The period of review under 37 CFR §1.777(c)(1), the testing period, was from August 18, 1987 to September 11, 1990, which is 3.07 years or 1121 days.

(ii) The period of review under 37 CFR §1.777(c)(2), the approval phase, was from September 11, 1990 to August 5, 1994, which is 3.90 years or 1425 days.

(b) The regulatory review period upon which the period of extension is calculated is the entire regulatory review period as determined in sub-paragraph 11(a) above (2545 days) less the sum of:

(i) The number of days in the regulatory period as set forth in §1.777(c)(1) and (2) which were on and before the date on which the patent issued ( $2545 - 686 = 1858$  days);

(ii) The number of days in the regulatory period as set forth in §1.777(c)(1) and (2) during which MBI did not act with due diligence, which is zero (0) days ( $1858 - 0 = 1858$ ); and

(iii) One-half the number of days remaining in the testing period as set forth in §1.777(c)(1) after the patent issued (July 4, 1989) ( $1121 - 687 = 434 \div 2 = 217$  days) ( $1858 - 217 = 1641$ );

which is a total of 4.49 years or 1641 days.

(c) The number of days as determined in 11(b) above, i.e., 1641 days, when added to the original term of the patent which is July 4, 2006 would result in the date December 31, 2010.

(d) The addition of fourteen (14) years to the date of approval of the application under §515 of the Federal Food, Drug and Cosmetic Act would result in the date August 5, 2008.

(e) When comparing 11(c) and (d) above, the earlier date is August 5, 2008.

(f) Since the original patent issued after September 24, 1984, and since no request for exemption under subsection (5)(f) of §515 of the Federal Food, Drug and Cosmetic Act was submitted before September 24, 1984, five (5) years when added to the original expiration date of the patent (July 4, 2006) would result in the date July 4, 2011.

(g) The earlier date when comparing 11(c) and (f) above is August 5, 2008.

Therefore, the length of extension of patent term claimed by MBI is 763 days or 2.09 years.

STATEMENT PURSUANT TO 37 CFR §1.740(a)(13)

(12) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to the application for extension.

(13) The prescribed fee for receiving and acting upon this application is enclosed. If any additional fees are due, authorization is given to charge our deposit account number 03-1952.

(14) Direct all inquiries and correspondence relating to this application to

Freddie K. Park  
Morrison & Foerster  
755 Page Mill Road  
Palo Alto, CA 94304  
Phone: (415) 813-5705  
Fax: (415) 494-0792

(15) A certified duplicate of this application is being submitted herewith.

(16) The requisite declaration pursuant to 37 CFR §1.740(b) is attached hereto as Appendix F.

Respectfully submitted,

By Freddie K. Park  
Freddie K. Park

Registration No. 35,636

Date September 21, 1994

MORRISON & FOERSTER  
755 Page Mill Road  
Palo Alto, CA 94304-1018  
(415) 813-5600  
Fax: (415) 494-0792



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Patent and Trademark Office

ASSISTANT SECRETARY AND CC  
OF PATENTS AND TRADEMARKS  
Washington, D.C. 20231

Exhibit A

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JUL 1 1988

TILTON, FALLON, LUNGWUS & CHESTNUT  
100 SO. WACKER DR.  
CHICAGO, IL 60606-4002

TILTON, FALLON, LUNGWUS,  
CHESTNUT

UNITED STATES PATENT AND TRADEMARK OFFICE  
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

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88

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF  
THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS  
AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME  
NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE  
AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 WIDDER, KENNETH J.  
ASSIGNOR: 002 WESTKAEMPER, PETER J.

DOC DATE: 12/29/87  
DOC DATE: 12/29/87

RECORDATION DATE: 01/21/88 NUMBER OF PAGES 001 REEL/FRAE 4834/0803

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 MOLECULAR BIOSYSTEMS, INC., SAN DIEGO, CA. A CORP. OF CA.

SERIAL NUMBER 7-139576 FILING DATE 12/29/87  
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: CONCENTRATED STABILIZED MICROBUBBLE-TYPE ULTRASONIC  
IMAGING AGENT

INVENTOR: 001 WIDDER, KENNETH J.  
INVENTOR: 002 WESTKAEMPER, PETER J.

SERIAL NUMBER 7-139576 FILING DATE 12/29/87  
PATENT NUMBER ISSUE DATE 00/00/00

TITLE OF INVENTION: CONCENTRATED STABILIZED MICROBUBBLE-TYPE ULTRASONIC  
IMAGING AGENT

INVENTOR: 001 WIDDER, KENNETH J.  
INVENTOR: 002 WESTKAEMPER, PETER J.

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EXHIBIT A

accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

☐ Other

139,578

Serial No. December 29, 1987

In consideration of One Dollar and other good and valuable considerations, the receipt of which is hereby acknowledged, the undersigned hereby assigns to Molecular Biosystems, Inc.  
(hereinafter referred to as "assignee"), a corporation of the State of California  
having a principal place of business at San Diego, California  
its successors and assigns the entire right, title and interest in the invention or improvements in Concentrated Stabilized Microbubble-Type Ultrasonic Imaging and in the application for Letters Patent of the United States therefor, executed by the undersigned on December 29, 1987, and in any renewal, extension, division or continuation of any Letters Patent that may be granted upon said application or applications.

The undersigned hereby authorize and request the Commissioner of Patents to issue said Letters Patent to said assignee.

For said considerations the undersigned hereby agree, upon the request of said assignee, its successors and assigns, to execute any and all divisional and renewal applications for said invention or improvements, and any necessary oath or supplemental oath or affidavits relating thereto, and any application for the release or extension of any Letters Patent that may be granted upon said application that said assignee, its successors or assigns may deem necessary or expedient, and for the said considerations the undersigned further agree upon the request of said assignee, its successors or assigns, in the event of said application or any division thereof, or Letters Patent issued thereon, or any release or application for the release thereof, becoming involved in interference, to cooperate fully with said assignee, its successors or assigns in the matters of preparing and executing the preliminary statement and giving and producing evidence in support thereof and hereby agree to perform, upon each request, any and all affirmative acts to obtain said Letters Patent and vest all rights therein hereby conveyed in the said assignee, its successors and assigns as fully and entirely as the same would have been held and enjoyed by the undersigned if this assignment and sale had not been made, and for the said considerations the undersigned hereby also assign to said assignee, its successors and assigns the entire right, title and interest in said invention or improvements for any and all foreign countries and agree upon the request of said assignee, its successors and assigns to execute any and all documents that shall be required of it, to be executed in connection with any and all applications for foreign Letters Patent therefor, including the prosecution thereof, and to execute any and all documents necessary to invent title in said foreign applications and patents in said assignee.

The foregoing Assignment shall be deemed fully executed and shall become effective this 29th day of December, 1987.

Kenneth J. Widdler (SEAL)  
Patricia J. Widdler (SEAL)  
\_\_\_\_ (SEAL)

RECORDED  
PATENT & TRADEMARK OFFICE

JAN 21 1988

RECEIVED  
JAN 16 1988

Exhibit B

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Patent of:  
Widder et al

Patent Number: 4,844,882

Issued: July 4, 1989

For: CONCENTRATED STABILIZED MICROBUBBLE-TYPE ULTRASONIC IMAGING  
AGENT

POWER OF ATTORNEY

The Honorable Commissioner of  
Patents and Trademarks  
BOX PATENT EXTENSION  
Washington, DC 20231

Dear Sir:

In the matter of the above-entitled application, I hereby  
revoke all power of Attorney heretofore given by me and appoint  
as my attorney Freddie K. Park, Reg. No. 35,636; Reid G. Adler,  
Reg. No. 30,988; Felissa H. Cagan, Reg. No. 35,089; Thomas E.  
Ciotti, Reg. No. 21,013; Patricia M. Drost, Reg. No. 29,790;  
Edward G. Durney, Reg. No. 37,611; Tyler Dylan, Reg. No. 37,612;  
Nancy Joyce Gracey, Reg. No. 28,216; Bill Kennedy, Reg. No.  
33,407; Paul C. Kimball, Reg. No. 34,641; Susan K. Lehnhardt,  
Reg. No. 33,943; Shmuel Livnat, Reg. No. 33,949; Gladys H.  
Monroy, Reg. No. 32,430; Kate H. Murashige, Reg. No. 29,959;  
Jackie N. Nakamura, Reg. No. 35,966; Paul F. Schenck, Reg. No.  
27,253; Lynn E. Schwenning, 37,233; James R. Shay, 32,062; Debra  
A. Shetka, Reg. No. 33,309; Cecily Anne Snyder, Reg. No. 37,448;  
E. Thomas Wheelock, Reg. No. 28,825; and Anna Lewak Wight, Reg.  
No. 33,006, all of Morrison & Foerster, 755 Page Mill Road, Palo  
Alto, California 94304, with full power of substitution,  
association and revocation, to prosecute said application and to  
transact all business in the Patent Office connected therewith.

EXHIBIT B

24843\2800000\165584.1

Please direct all telephone calls to Freddie K. Park at telephone number (415) 813-5600.

MOLECULAR BIOSYSTEMS, INC.  
Assignee of Record

Dated: September 19, 1994

By



Name: Steven Lawson

Title: Vice President, Legal Affairs

CERTIFICATE OF MAILING BY "EXPRESS MAIL"

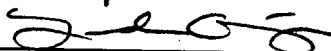
"Express Mail" mailing label number TB 028723310 US

Date of Deposit September 21, 1994

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of patents and Trademarks, Washington, D.C. 20231

LINDA QUINONEZ

(Typed or printed name of person mailing paper or fee)



(Signature of person mailing paper or fee)

CERTIFICATE UNDER 37 CFR 3.73(b)

Applicant: Widder et al

Patent No.: 4,844,882 Issued: July 4, 1989

For: CONCENTRATED STABILIZED MICROBUBBLE-TYPE ULTRASONIC IMAGING AGENT

MOLECULAR BIOSYSTEMS, INC., a

(Name of Assignee)

CORPORATION

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

certifies that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of either:

A. ☒ An assignment from the inventor(s) of the patent application identified above. The assignment was recorded in the Patent and Trademark Office at Reel 4834, Frame 0803, or for which a copy thereof is attached.

OR

B. ☐ A chain of title from the inventor(s), of the patent application identified above, to the current assignee as shown below:

1. From: To:

The document was recorded in the Patent and Trademark Office at Reel , Frame , or for which a copy thereof is attached.

2. From: To:

The document was recorded in the Patent and Trademark Office at Reel , Frame , or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet.

☒ Copies of assignments or other documents in the chain of title are attached.

The undersigned has reviewed all the documents in the chain of title of the patent application identified above and, to the best of undersigned's knowledge and belief, title is in the assignee identified above.

The undersigned (whose title is supplied below) is empowered to act on behalf of the assignee.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: September 19, 1994

Name: Steven Lawson

Title: Vice President, Legal Affairs

Signature: 



139,578

Serial No. December 29, 1987

In consideration of One Dollar and other good and valuable considerations, the receipt of which is hereby acknowledged, the undersigned hereby assigns to Molecular Biosystems, Inc.  
 (hereinafter referred to as "assignee"), a corporation of the State of California  
 having a principal place of business at San Diego, California  
 its successors and assigns the entire right, title and interest in the invention or improvements in Concentrated Stabilized Microbubble-Type Ultrasonic Imaging and in the application for Letters Patent of the United States therefor, executed by the undersigned on December 29, 1987, and in any renewals, extension, division or continuation of any Letters Patent that may be granted upon said application or applications.

The undersigned hereby authorizes and request the Commissioner of Patents to issue said Letters Patent to said assignee.

For said considerations the undersigned hereby agree, upon the request of said assignee, its successors and assigns, to execute any and all divisional and renewal applications for said invention or improvements, and any necessary oath or supplemental oath or affidavit relating thereto, and any application for the release or extension of any Letters Patent that may be granted upon said application that said assignee, its successors or assigns may deem necessary or expedient, and for the said considerations the undersigned further agree upon the request of said assignee, its successors or assigns, in the event of said application or any division thereof, or Letters Patent issued thereon, or any release or application for the release thereof, becoming involved in interference, to cooperate fully with said assignee, its successors or assigns in the matters of preparing and executing the preliminary statement and giving and producing evidence in support thereof and hereby agree to perform, upon such request, any and all affirmative acts to obtain said Letters Patent and vest all rights therein hereby conveyed in the said assignee, its successors and assigns as fully and entirely as the same would have been held and enjoyed by the undersigned if this assignment and sale had not been made, and for the said considerations the undersigned hereby also assign to said assignee, its successors and assigns the entire right, title and interest in said invention or improvements for any and all foreign countries and agree upon the request of said assignee, its successors and assigns to execute any and all documents that shall be required of it, to be executed in connection with any and all applications for foreign Letters Patent therefor, including the prosecution thereof, and to execute any and all documents necessary to invent title in said foreign applications and patents in said assignee.

The foregoing Assignment shall be deemed fully executed and shall become effective this 29th day of December, 1987.

Kenneth J. Widdler (SEAL)  
Patricia J. Widdler (SEAL)  
 \_\_\_\_\_ (SEAL)

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 PATENT & TRADEMARK OFFICE

JAN 21 1988

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 JAN 21 1988

# United States Patent [19]

Widder et al.

[11] Patent Number: 4,844,882

[45] Date of Patent: Jul. 4, 1989

## [54] CONCENTRATED STABILIZED MICROBUBBLE-TYPE ULTRASONIC IMAGING AGENT

[75] Inventors: Kenneth J. Widder, Del Mar; Peter J. Westkaemper, San Diego, both of Calif.

[73] Assignee: Molecular Biosystems, Inc., San Diego, Calif.

[21] Appl. No.: 139,576

[22] Filed: Dec. 29, 1987

[51] Int. Cl.<sup>4</sup> ..... A61K 49/00

[52] U.S. Cl. .... 424/9; 514/945;  
128/660.01

[58] Field of Search ..... 424/9; 514/945;  
128/660-663

## [56] References Cited

### U.S. PATENT DOCUMENTS

4,276,885	7/1981	Tickner et al.	128/660
4,466,442	8/1984	Hilman et al.	128/653
4,572,203	2/1986	Feinstein	128/661
4,718,433	1/1988	Feinstein	128/660
4,774,958	10/1988	Feinstein	128/660.01

## OTHER PUBLICATIONS

Tickner et al., National Technical Information Service Report HR 62917-1A, Apr. 1977, pp. 34-40.

Feinstein et al., (1984), J. Am. Coll. Cardio., 3:14-20.

Keller et al., (1987), Amer. Heart J., 114:570-575.

Primary Examiner—Douglas W. Robinson

Assistant Examiner—Raymond J. Henley, III

Attorney, Agent, or Firm—Tilton, Fallon, Lungmus & Chestnut

## [57] ABSTRACT

A microbubble-type ultrasonic imaging agent is provided comprising a parenterally-administerable aqueous medium containing a dispersion of microspheres predominantly of diameters less than 10 microns, wherein the microspheres consist of gas microbubbles encapsulated with water-insolubilized biocompatible material. The imaging agent is characterized by having a concentration of greater than  $100 \times 10^6$  microspheres per milliliter, and a stability such that this concentration is maintained for over 4 weeks at a temperature of 20° to 25° C.

8 Claims, 4 Drawing Sheets

EXHIBIT C



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS  
Washington, D. C. 20231

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000131

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DATE MAILED  
10/29/92

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## MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY SML YR ENT	STAT
1	4,844,882	283	450	----	07/139,576	07/04/89	12/29/87	04 YES	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (\*) will appear in the "status" column. Where an asterisk (\*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

EXHIBIT D

ITM  
NBR

ATTY DKT  
NUMBER

1

UIA4

PLEASE RETURN THIS NOTICE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO:

Exhibit E

DATE	SUBJECT MATTER	ACTIVITY	COMMENTS
8/18/87	IDE G870144 ORIGINAL	Submission to FDA	Submission of Original IDE containing Protocol 12001
8/24/87	IDE G870144	Letter from FDA	FDA receipt of IDE and assignment of IDE number
9/1/87	IDE G870144 Amendment 1	Submission to FDA	Request for literature references
9/18/87	IDE G870144	Letter from FDA	Request for additional information regarding Protocol 12001
10/13/87	IDE G870144	Letter from FDA	Letter stating that product would be reviewed as a device
10/20/87	IDE G870144 Amendment 2	Submission to FDA	Response to 9/18/87 letter from FDA
11/20/87	IDE G870144 Amendment 2	Letter from FDA	Request for additional information regarding Protocol 12001
12/9/87	IDE G870144 Amendment 3	Submission to FDA	Response to 11/20/87 letter from FDA
1/14/88	IDE G870144 Amendment 3	Letter from FDA	Request for additional information regarding Protocol 12001
1/22/88	IDE G870144 Supplement 1	Submission to FDA	Response to 1/14/88 letter from FDA
2/3/88	IDE G870144	Telephone Call with FDA	Discussion regarding 9/18/87 letter from FDA
2/8/88	IDE G870144 Supplement 2	Submission to FDA	Follow-up to 2/3/88 telephone call with FDA
2/23/88	IDE G870144 Amendment 3	Letter from FDA	Conditional approval of Protocol 12001 and request for additional information
4/13/88	IDE G870144 Supplement 3	Submission to FDA	Addition of new investigator to Protocol 12001
4/22/88	IDE G870144 Supplement 4	Submission to FDA	Addition of Protocol 12002
5/12/88	IDE G870144 Supplement 5	Submission to FDA	Addition of Protocol 12003
5/13/88	IDE G870144 Supplement 4	Letter from FDA	Request for additional information regarding Protocol 12002
5/27/88	IDE G870144 Supplement 6	Submission to FDA	Response to 5/13/88 letter from FDA
6/9/88	IDE G870144 Supplement 5	Letter from FDA	Request for additional information regarding Protocol 12003
6/15/88	IDE G870144 Supplement 7	Submission to FDA	Progress Report and request for approval of Protocol 12002, and addition of Protocol 12005
6/15/88	IDE G870144	Letter from FDA	Request for additional information regarding Protocol 12002
6/23/88	Supplement 4	Letter from FDA	Conditional approval of Protocols 12001 and 12002
7/11/88	IDE G870144 Supplement 8	Submission to FDA	Notification of internal review board approval for Protocol 12001 and request to add second site
7/15/88	IDE G870144 Supplement 6	Letter from FDA	Request for additional information regarding Protocol 12002

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7/24/88	IDE G870144	Letter to FDA	Request for permit to export to the Netherlands
8/4/88	IDE G870144 Supplement 8	Letter from FDA	Approval to add second site to Protocol 12001
9/8/88	IDE G870144	Letter from FDA	Notification that clinical trials in the Netherlands could be acceptable
9/21/88	IDE G870144 Supplement 9	Submission to FDA	Progress Report and response to 7/15/88 letter from FDA
10/21/88	IDE G870144	Letter from FDA	Conditional approval of Protocol 12005 and request for additional information
11/16/88	IDE G870144 Supplement 10	Submission to FDA	Response to 10/21/88 letter from FDA
12/16/88	IDE G870144	Letter from FDA	Approval of Protocol 12005
12/16/88	IDE G870144	Telephone Call with FDA	Request for a meeting to review facility plans with FDA
1/10/89	IDE G870144 Supplement 11	Submission to FDA	Addition of investigators and sites to Protocol 12005
1/11/89	IDE G870144	Meeting with FDA	Meeting with FDA regarding facility plans
1/11/89	IDE G870144 Supplement 12	Submission to FDA	Correction to 1/10/89 submission to FDA
1/24/89	IDE G870144	Meeting with FDA	Discussion regarding manufacturing process
2/9/89	IDE G870144 Supplement 11	Telephone Call with FDA	Request for status of 1/10/89 submission to FDA
2/9/89	IDE G870144 Supplement 11 & 12	Letter from FDA	Conditional approval of Protocol 12005 as supplemented on 1/10/89 and request for additional information
2/9/89	IDE G870144	Telephone Call with FDA	Inquiry into which OB/Gyn division would review IDE
2/23/89	IDE G870144 Supplement 13	Submission to FDA	Response to 2/9/89 letter from FDA
2/23/89	IDE G870144	Telephone Call with FDA	Discussion regarding clinical investigations
2/28/89	IDE G870144	Telephone Call from FDA	Follow-up to 2/23/89 telephone call with FDA
3/18/89	IDE G870144 Supplement 11 & 13	Telephone Call with FDA	Discussion regarding 1/10/89 and 2/23/89 submissions to FDA
3/20/89	IDE G870144 Supplement 13	Letter from FDA	Conditional approval of Protocol 12005 and request for additional information
3/20/89	IDE G870144 Supplement 13	Telephone Call with FDA	Discussion regarding 3/20/89 letter from FDA
4/4/89	IDE G870144	Letter to FDA	Request for permit to export to Japan
4/4/89	IDE G870144	Letter to FDA	Request for permit to export to the Netherlands
4/7/89	IDE G870144 Supplement 14	Submission to FDA	Notification of current list of investigators
4/11/89	IDE G870144	Letter to FDA	Request for permit to export to Norway
4/14/89	IDE G870144	Letter from FDA	Acknowledgement of receipt of 4/4/89 and 4/5/89 letters regarding requests for permit to export to Japan and the Netherlands
4/14/89	IDE G870144	Telephone Call with FDA	Request for meeting with FDA regarding status of IDE
4/20/89	IDE G870144 Supplement 15	Submission to FDA	Request to extend deadline to respond to 3/20/89 letter from FDA

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5/2/89	IDE G870144 Supplement 13	Meeting at FDA	Discussion regarding 3/20/89 letter from FDA
5/5/89	IDE G870144	Letter from FDA	Notification that processing of requests takes 4-6 weeks after receipt by FDA
5/16/89	IDE G870144 Supplement 13	Telephone Call with FDA	Request for minutes of 5/2/89 meeting with FDA
5/16/89	IDE G870144 Supplement 13	Letter to FDA	Minutes of 5/2/89 meeting with FDA
5/16/89	IDE G870144 Supplement 15	Letter from FDA	Approval of request to extend deadline for response to 3/20/89 letter from FDA
5/18/89	IDE G870144	Letter to FDA	Request for status of export permit to the Netherlands
5/24/89	IDE G870144	Letter from FDA	Approval of request for permit to export to Japan and Norway
5/28/89	IDE G870144	Letter from FDA	Export permits for Japan and Norway
6/5/89	IDE G870144 Supplement 16	Submission to FDA	Response to 3/20/89 letter from FDA
6/6/89	IDE G870144 Supplement 17	Submission to FDA	Progress Report
6/22/89	IDE G870144 Supplement 18	Submission to FDA	Progress Report
6/23/89	IDE G870144 Supplement 16 & 17	Telephone Call with FDA	Discussion regarding clinical protocols
6/29/89	IDE G870144 Supplement 19	Submission to FDA	Addition of Protocol 12007
7/11/89	IDE G870144 Supplement 20	Submission to FDA	Addition of Protocol 12006
7/14/89	IDE G870144	Letter from FDA	Notification of FDA relocation
7/14/89	IDE G870144 Supplement 16	Letter from FDA	Approval of Protocol 12005
8/11/89	IDE G870144 Supplement 18	Letter from FDA	Acknowledgement of receipt of 6/22/89 submission to FDA and request for additional information
8/16/89	IDE G870144 Supplement 19 & 20	Letter from FDA	Conditional approval of Protocols 12006 and 12007 and request for additional information
9/14/89	IDE G870144	Meeting at FDA	Discussion regarding PMA, termination of Protocol 12003 and changes to Protocols 12006 and 12007
9/21/89	IDE G870144 Supplement 21	Submission to FDA	Response to 8/11/89 letter from FDA regarding 6/22/89 submission to FDA
9/28/89	IDE G870144 Supplement 22	Submission to FDA	Response to 8/16/89 Letter from FDA regarding Protocols 12006 and 12007
10/17/89	IDE G870144	Meeting at FDA	Discussion regarding software analysis of ultrasound images
10/20/89	IDE G870144	Letter from FDA	Conditional approval of Protocol 12006 and request for additional information
10/20/89	IDE G870144	Telephone Call with FDA	Arrange for meeting at FDA regarding software analysis of ultrasound images

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11/2/89	IDE G870144 Supplement 23	Submission to FDA	Request for change to manufacturing process
11/17/89	IDE G870144 Supplement 23	Telephone Call with FDA	Request for status of 11/2/89 submission to FDA and request for meeting at FDA to discuss
11/20/89	IDE G870144 Supplement 22	Letter from FDA	Approval of Protocol 12007
11/28/89	IDE G870144	Meeting at FDA	Discussion regarding 11/2/89 submission to FDA
12/4/89	IDE G870144 Supplement 24	Submission to FDA	Addition of Protocol 12004
12/6/89	IDE G870144 Supplement 25	Submission to FDA	Request to expand Protocol 12007 to additional patients
12/10/89	IDE G870144	Letter from FDA	Request for additional information regarding export permit to the Netherlands
12/29/89	IDE G870144 Supplement 23	Letter from FDA	Approval of change to manufacturing process as requested in 11/2/89 submission to FDA
12/29/89	IDE G870144 Supplement 24	Letter from FDA	Approval of Protocol 12004 as amended in 12/4/89 submission to FDA
1/4/90	IDE G870144 Supplement 26	Submission to FDA	Addition of Protocol 13289
2/5/90	IDE G870144 Supplement 25	Letter from FDA	Approval of request to expand Protocol 12007 to additional patients as requested in 12/6/89 submission to FDA
2/7/90	IDE G870144 Supplement 27	Submission to FDA	Summary of clinical investigators and sites
2/9/90	IDE G870144 Supplement 28	Submission to FDA	Information regarding animal studies
2/12/90	IDE G870144 Supplement 26	Letter from FDA	Conditional approval of Protocol 13289 and request for additional information
2/22/90	IDE G870144	Telephone Call from FDA	Request for minutes of 11/17/89 meeting at FDA
2/22/90	IDE G870144	Letter to FDA	Request for permit to export to Japan
3/14/90	IDE G870144	Letter to FDA	Request for permit to export to Japan
3/16/90	IDE G870144 Supplement 29	Submission to FDA	Response to 2/12/90 letter from FDA
3/21/90	IDE G870144	Telephone Call with FDA	Discussion regarding 2/9/90 submission to FDA
3/21/90	IDE G870144	Letter to FDA	Request for permit to export to the Netherlands
4/3/90	IDE G870144	Letter to FDA	Request for permit to export to Norway
4/18/90	IDE G870144 Supplement 29	Letter from FDA	Conditional approval of Protocol 13289 and request for additional information
4/18/90	IDE G870144	Telephone Call with FDA	Discussion regarding status of IDE and upcoming meeting with FDA
4/18/90	IDE G870144	Letter from FDA	Approval of request for permit to export to Japan
5/11/90	IDE G870144 Supplement 30	Submission to FDA	Response to 4/18/90 Letter from FDA regarding Protocol 13289
5/18/90	IDE G870144 Supplement 31	Submission to FDA	Correction to 5/11/90 submission to FDA

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6/1/90	IDE G870144 Supplement 32	Submission to FDA	Progress Report
6/5/90	IDE G870144 Supplement 33	Submission to FDA	Correction to 6/1/90 submission to FDA
6/12/90	PMA P900059	Letter to FDA	Agenda for upcoming meeting with FDA
6/14/90	IDE G870144 Supplement 30 & 31	Letter from FDA	Conditional approval of Protocol 13289 and request for additional information
6/20/90	PMA	Telephone Call with FDA	Discussion upcoming meeting with FDA
6/27/90	PMA	Meeting with FDA	Discussion regarding filing of PMA
7/3/90	IDE G870144 Supplement 30 & 31	Letter from FDA	Approval of Protocol 13289 and request for additional information
7/5/90	IDE G870144 Supplement 33	Letter from FDA	Comments on 6/1/90 and 6/5/90 submissions to FDA
7/9/90	IDE G870144	Telephone Call with FDA	Discussion regarding clinical information
7/17/90	PMA	Telephone Call with FDA	Follow-up to 6/27/90 meeting with FDA
7/24/90	IDE G870144	Telephone Call with FDA	Discussion regarding export request for Norway
7/24/90	IDE G870144	Letter to FDA	Request for permit to export to the Netherlands
8/2/90	IDE G870144	Letter to FDA	Request for permit to export to Norway
8/2/90	IDE G870144	Letter from FDA	Request for manufacturing and clinical information
9/11/90	PMA P900059 ORIGINAL	Submission to FDA	Submission of Original PMA
9/13/90	IDE G870144 Supplement 34	Submission to FDA	Response to 7/3/90 letter from FDA
9/13/90	IDE G870144 Supplement 35	Submission to FDA	See IDE G870144/Supplement 34: Logged in by FDA as Supplement 35
9/17/90	IDE G870144	Letter from FDA	Request for additional information regarding 6/1/90 Progress Report
9/26/90	PMA P900059	Telephone Call with FDA	Discussion regarding PMA
9/27/90	PMA P900059	Telephone Call with FDA	Request for status of 9/13/90 submission to FDA
9/28/90	PMA P900059	Telephone Call with FDA	Request for status of PMA
9/28/90	PMA P900059 Amendment 1	Submission to FDA	Follow-up to 9/26/90 telephone call with FDA
10/2/90	PMA P900059 Amendment 2	Submission to FDA	Additional follow-up to 9/26/90 telephone call with FDA
10/11/90	PMA P900059	Telephone Call with FDA	Discussion regarding status of PMA
10/12/90	PMA P900059	Telephone Call with FDA	Discussion regarding status of PMA
10/16/90	PMA P900059	Telephone Call with FDA	Discussion regarding use of statistical data in PMA
10/19/90	PMA P900059	Telephone Call with FDA	Additional discussion regarding use of statistical data in PMA
10/22/90	PMA P900059	Telephone Call with FDA	Request for status of internal FDA meeting regarding PMA
10/23/90	PMA P900059	Telephone Call with FDA	Discussion regarding manufacturing process and status of "fileability" of PMA
10/24/90	PMA P900059	Telephone Call with FDA	Additional discussion regarding manufacturing process
10/26/90	PMA P900059	Telephone Call with FDA	Additional discussion regarding manufacturing process

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10/30/90	PMA P900059	Telephone Call with FDA	Request for status of "fileability" of PMA
11/19/90	PMA P900059	Letter from FDA	Notification of "fileable" status of PMA and request for additional information
11/27/90	PMA P900059	FAX to FDA	Proposed outline for amendment to statistical data used in PMA
11/28/90	PMA P900059	Telephone Call with FDA	Discussion regarding response to 11/20/90 letter from FDA
12/10/90	PMA P900059	Telephone Call with FDA	Discussion regarding status of IDE and response to 11/20/90 letter from FDA
12/17/90	IDE G870144	Letter from FDA	Denial of request for permit to export to Norway
1/15/91	IDE G870144	Telephone Call with FDA	Notification that request for permit to export to Norway was denied
2/1/91	PMA P900059	Telephone Call with FDA	Notification of change of PMA reviewer at FDA
2/1/91	PMA P900059 Amendment 3	Submission to FDA	Response to 11/19/90 letter from FDA
2/13/91	PMA P900059	FAX to FDA	Request for status of PMA scientific review
2/22/91	PMA P900059	FAX from FDA	Notification of change of FDA reviewing division from cardiovascular to OB/Gyn
2/25/91	PMA P900059	Telephone Call with FDA	Discussion regarding review of PMA by OB/Gyn
2/26/91	PMA P900059	Letter to FDA	Agenda for 2/28/91 meeting at FDA
2/28/91	PMA P900059	Meeting at FDA	Discussion regarding status of PMA
3/4/91	PMA P900059	Telephone Call with FDA	Review of 2/28/91 meeting at FDA
3/25/91	PMA P900059	Telephone Call with FDA	Request for status of PMA
3/25/91	PMA P900059 Amendment 4	Submission to FDA	Additional information regarding 2/1/91 submission to FDA
3/27/91	IDE G870144	Letter from FDA	Approval of request for permit to export to the Netherlands
4/15/91	IDE G870144	Letter from FDA	Approval of request for permit to export to Norway
4/22/91	IDE G870144 Supplement 36	Submission to FDA	Addition of Protocol 13191
5/1/91	PMA P900059	Telephone Call with FDA	Notification that review of PMA would take place in 90 days
5/3/91	PMA P900059	Telephone Call with FDA	Discussion regarding status of PMA
5/3/91	PMA P900059	Letter to FDA	Comments regarding review of PMA
5/6/91	PMA P900059	Telephone Call with FDA	Request for status of PMA
5/23/91	PMA P900059	Telephone Call with FDA	Request for status of PMA and inquiry regarding panel meeting
5/23/91	PMA P900059	Telephone Call with FDA	Request for status of PMA
5/23/91	IDE G870144 Supplement 36	Letter from FDA	Conditional approval of Protocol 13191 and request for additional information
5/24/91	PMA P900059	Telephone Call with FDA	Notification of intent to send PMA "filed" letter and report on status of review of Protocol 13191
5/31/91	PMA P900059 Amendment 5	Submission to FDA	Notification regarding product licensee
6/7/91	IDE G870144 Supplement 37	Submission to FDA	Addition of Protocol 13291

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6/7/91	IDE G870144 Supplement 38	Submission to FDA	Response to 5/23/91 letter from FDA
6/10/91	PMA P900059	Letter from FDA	Receipt of PMA "Filed" letter
6/11/91	IDE G870144 Supplement 39	Submission to FDA	Progress Report
6/11/91	PMA P900059 Amendment 6	Submission to FDA	Notification of official PMA correspondents at MBI
6/14/91	PMA P900059 Amendment 7	Letter to FDA	Progress Report
6/14/91	PMA P900059	Telephone Call with FDA	Request for status of PMA
6/18/91	PMA P900059	Telephone Call with FDA	Request for status of PMA
6/20/91	PMA P900059	Letter from FDA	Request for additional information
6/20/91	PMA P900059	Telephone Call with FDA	Request for discussion with FDA regarding 6/20/91 letter from FDA
6/20/91	PMA P900059	Telephone Call with FDA	Discussion regarding 6/20/91 letter from FDA
7/11/91	IDE G870144 Supplement 37	Letter from FDA	Conditional approval of Protocol 13291 and request for additional information
7/11/91	PMA P900059	Letter from FDA	Request for additional information
7/23/91	IDE G870144 Supplement 36	Letter from FDA	Approval of Protocol 13191
8/7/91	PMA P900059	Telephone Call with FDA	Discussion regarding 7/11/91 letter from FDA and request for status of PMA
8/7/91	PMA P900059	Telephone Call with FDA	Arrange for telephone call with FDA regarding 6/20/91 letter from FDA
8/8/91	PMA P900059	Telephone Call with FDA	Discussion regarding 6/20/91 and 7/11/91 letters from FDA
8/8/91	PMA P900059 Amendment 8	Submission to FDA	Minutes from 8/8/91 telephone call with FDA
8/9/91	IDE G870144 Supplement 40	Submission to FDA	Response to 7/11/91 letter from FDA
9/11/91	PMA P900059	Telephone Call with FDA	Request for information regarding PMA panel meeting
9/11/91	IDE G870144 Supplement 40	Letter from FDA	Approval of Protocol 13291
9/30/91	PMA P900059 Amendment 9	Submission to FDA	Additional response to 6/20/91 letter from FDA
10/17/91	PMA P900059	Telephone Call with FDA	Request for information regarding PMA panel meeting
10/25/91	PMA P900059 Amendment 10	Submission to FDA	Correction to 9/30/91 submission to FDA
11/19/91	IDE G870144 Supplement 41	Submission to FDA	Request for change to packaging specifications
12/2/91	IDE G870144 Supplement 42	Submission to FDA	Addition of Protocol 13391
12/2/91	PMA P900059	Telephone Call with FDA	Request for status of PMA and information regarding panel meeting
12/13/91	PMA P900059	Telephone Call with FDA	Discussion regarding status of PMA and panel meeting

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12/13/91	IDE G870144 Supplement 43	Submission to FDA	Additional information regarding clinical studies
12/20/91	IDE G870144 Supplement 41	Telephone Call with FDA	Request for additional information regarding 11/19/91 submission to FDA
12/20/91	IDE G920008 Original	Submission to FDA	Addition of Protocol 13491
12/20/91	IDE G870144 Supplement 41	Letter from FDA	Conditional approval of 11/19/91 submission to FDA and request for additional information
12/27/91	IDE G870144 Supplement 42	Letter from FDA	Conditional approval of Protocol 13391 and request for additional information
1/13/92	IDE G870144 Supplement 43	Letter from FDA	Comments regarding 12/13/91 submission to FDA
1/15/92	IDE G920008	Letter from FDA	Assignment of IDE number to Protocol 13491
1/21/92	IDE G870144 Supplement 44	Submission to FDA	Response to 12/27/91 letter from FDA
1/22/92	IDE G870144 Supplement 41 IDE G920008 PMA P900059	Telephone Call with FDA	Discussion regarding 12/20/91 letter from FDA, Protocol 13491 and request for status of PMA
1/24/92	PMA P900059	Telephone Call with FDA	Discussion regarding status of PMA
1/24/92	IDE G870144 Supplement 45	Submission to FDA	Response to 12/20/91 letter from FDA
1/29/92	IDE G920008	Letter from FDA	Request for additional information regarding Protocol 13491
2/4/92	IDE G870144 Supplement 46	Submission to FDA	Progress Report
2/12/92	IDE G870144 Supplement 44	Letter from FDA	Request for additional information regarding Protocol 13391
2/24/92	PMA P900059	Telephone Call with FDA	Request for status of PMA
2/25/92	IDE G870144 Supplement 45	Letter from FDA	Approval of 11/19/91 submission to FDA
2/25/92	PMA P900059	Letter to FDA	Agenda for 3/16/92 meeting at FDA regarding PMA review and panel meeting
2/28/92	PMA P900059	Telephone Call with FDA	Arrangemts for meeting at FDA
2/28/92	IDE G920008 Amendment 1	Submission to FDA	Response to 1/29/92 letter from FDA
3/6/92	IDE G870144 Supplement 46	Letter from FDA	Acknowledgement of receipt of Progress Report dated 2/4/92
3/13/92	PMA P900059	Telephone Call with FDA	Discussion regarding upcoming meeting at FDA
3/13/92	IDE G870144 Supplement 47	Submission to FDA	Response to 2/12/92 letter from FDA
3/16/92	PMA P900059	Meeting with FDA	Discussion regarding status of PMA and upcoming panel meeting
3/21/92	PMA P900059	Letter to FDA	Minutes from 3/16/92 meeting at FDA
3/31/92	PMA P900059	Telephone Call with FDA	Discussion regarding facility inspections
3/31/92	IDE G920008 Amendment 1	Letter from FDA	Request for additional information regarding Protocol 13491

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4/6/92	PMA P900059	Telephone Call with FDA	Discussion regarding status of PMA and upcoming panel meeting
4/6/92	PMA P900059	Letter from FDA	Updated status of PMA
4/17/92	PMA P900059	Letter from FDA	Notification regarding PMA status and upcoming panel meeting
4/17/92	IDE G870144	Letter from FDA	Approval of Protocol 13391
5/11/92	PMA P900059 Amendment 11	Submission to FDA	Progress Report
5/14/92	PMA P900059	Telephone Call with FDA	Discussion regarding panel meeting
6/4/92	PMA P900059 Amendment 11	Telephone Call with FDA	Acknowledgement of receipt of 5/11/92 Progress Report and discussion regarding panel meeting
6/11/92	PMA P900059 Amendment 3	Telephone Call with FDA	Request for update regarding panel meeting and status of PMA
6/29/92	PMA P900059	Telephone Call with FDA	Request for information regarding panel meeting
7/2/92	IDE G870144 Supplement 48	Submission to FDA	Progress Report
7/10/92	PMA P900059	Telephone Call with FDA	Request for information regarding panel meeting
7/10/92	PMA P900059 Amendment 3	Letter to FDA	Request for information regarding panel meeting
7/14/92	PMA P900059	Panel Meeting	Review of PMA by Radiologic Device Advisory Panel
7/20/92	PMA P900059 Amendment 3	FAX to FDA	Request for minutes from 7/14/92 panel meeting
7/20/92	PMA P900059 Amendment 12	Submission to FDA	Transmittal of tapes from 7/14/94 panel meeting
8/3/92	IDE G920008 Amendment 2	Submission to FDA	Response to 3/31/92 letter from FDA
8/5/92	IDE G870144 Supplement 49	Submission to FDA	Information regarding manufacturing process
8/5/92	IDE G870144	Letter from FDA	Acknowledgement of receipt of 7/2/92 Progress Report
8/12/92	PMA P900059	Telephone Call with FDA	Request for status of PMA
8/12/92	PMA P900059	Telephone Call with FDA	Discussion regarding product labeling requirements
8/19/92	PMA P900059	Telephone Call with FDA	Request for status of PMA
8/20/92	PMA P900059	Telephone Call with FDA	Request for status of PMA
8/24/92	IDE G870144 Supplement 49	Letter from FDA	Acknowledgement of receipt of 8/5/92 submission to FDA
8/27/92	PMA P900059	Telephone Call with FDA	Request for status of PMA
8/28/92	PMA P900059	Telephone Call with FDA	Request for status of PMA and discussion of post-market approval clinical studies
9/3/92	IDE G920008 Amendment 2	Letter from FDA	Request for additional information regarding Protocol 13491
9/4/92	PMA P900059	Telephone Call with FDA	Discussion regarding technical references
9/16/92	IDE G920008 Amendment 2	Telephone Call with FDA	Discussion regarding 9/3/92 letter from FDA

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9/17/92	PMA P900059	Telephone Call with FDA	Request for status of PMA
9/18/92	IDE G920008 Amendment 2	Telephone Call with FDA	Additional discussion regarding 9/3/92 letter from FDA
9/21/92	IDE G920008 Amendment 3	Submission to FDA	Response to 9/3/92 letter from FDA
9/23/92	IDE G920008 Amendment 3	Telephone Call with FDA	Discussion regarding Protocol 13491
9/29/92	PMA P900059	FAX to FDA	Request for informal review of post-market approval clinical studies
9/29/92	PMA P900059	Telephone Call with FDA	Request for status of PMA
9/30/92	PMA P900059	Telephone Call with FDA	Confirmation of 10/2/92 meeting at FDA
10/2/92	PMA P900059 IDE G920008 Amendment 3	Meeting at FDA	Discussion regarding post-market approval clinical studies and Protocol 13491
10/4/92	PMA P900059	Telephone Call with FDA	Request for status of PMA
10/5/92	PMA P900059	Telephone Call with FDA	Request for status of PMA
10/12/92	IDE G920187 Original	Submission to FDA	Addition of Protocol 13192
10/16/92	PMA P900059	Letter to FDA	Draft post-market approval clinical study protocol
10/16/92	IDE G920187	Letter from FDA	Acknowledgment of receipt of Protocol 13192
10/22/92	PMA P900059	Letter to FDA	Request for informal review of draft post-market approval clinical study protocol as submitted on 10/16/92
10/22/92	IDE G920008	Letter from FDA	Approval of Protocol 13491
10/26/92	PMA P900059 Amendment 13	Submission to FDA	Progress Report
10/30/92	PMA P900059	Telephone Call with FDA	Request for status of PMA
11/3/92	IDE G920008 Supplement 1	Submission to FDA	Request for additional study site for Protocol 13491
11/9/92	PMA P900059	Telephone Call with FDA	Request for status of PMA
11/10/92	PMA P900059	Telephone Call with FDA	Request for status of PMA
11/10/92	PMA P900059	Telephone Call with FDA	Discussion regarding export to Japan
11/10/92	IDE G920008	Telephone Call with FDA	Confirmation that 11/3/92 submission to FDA was correctly logged in as Supplement 1 and not Amendment 4
11/10/92	PMA P900059	Telephone Call with FDA	Request for status of PMA
11/10/92	IDE G870144 Supplement 50	Submission to FDA	Request for changes to Protocol 13291
11/11/92	IDE G920187	Letter from FDA	Request for additional information regarding Protocol 13192
11/12/92	IDE G920008	Letter from FDA	Request for additional information regarding Protocol 13491
11/13/92	PMA P900059 IDE G920187	Telephone Call with FDA	Request for status of PMA and Protocol 13192
11/17/92	PMA P900059	Telephone Call with FDA	Request for status of PMA
11/17/92	IDE G920187	Telephone Call with FDA	Discussion regarding 11/12/92 letter from FDA
11/18/92	PMA P900058	Letter from FDA	Request for additional information
11/18/92	PMA P900059	Telephone Call with FDA	Request for meeting at FDA

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11/19/92	PMA P900059 IDE G920187	FAX to FDA	Agenda for upcoming meeting at FDA
11/23/92	PMA P900059 IDE G920187	Meeting with FDA	Discussion regarding status of PMA and Protocol 13192
11/24/92	PMA P900059 G920187	Letter to FDA	Minutes from 11/23/92 meeting with FDA
11/25/92	PMA P900059 IDE G920008 Supplement 1	Telephone Call with FDA	Discussion regarding 11/18/92 letter from FDA
12/3/92	PMA P900059	Submission to FDA	Request to add clinical site to Protocol 13491
12/4/92	PMA P900059	Telephone Call with FDA	Discussion regarding post-market approval clinical studies and request for meeting at FDA
12/7/92	PMA P900059	Telephone Call with FDA	Discussion regarding post-market approval clinical study protocols
12/7/92	IDE G920008 Supplement 1	Letter from FDA	Approval of additional clinical site for Protocol 13491
12/11/92	IDE G870144 Supplement 50	Letter from FDA	Approval of Protocol 13291 as amended 11/10/92
12/15/92	PMA P900059	Telephone Call with FDA	Discussion regarding manufacturing process
12/30/92	PMA P900059 Amendment 14	Submission to FDA	Response to 11/18/92 letter from FDA
1/6/93	IDE G920187 Amendment 1	Submission to FDA	Response to 11/11/92 letter from FDA and request for change to packaging specifications (Note: only logged in by FDA for IDE G920187)
1/16/93	PMA P900059 Amendment 14	Telephone Call from FDA	Discussion regarding 12/30/93 submission to FDA
1/22/93	PMA and All IDE's	Telephone Call with FDA	Discussion regarding packaging information
1/27/93	PMA P900059	Telephone Call with FDA	Discussion regarding export to Japan
1/28/93	IDE G870144 Supplement 51 IDE G920008 Supplement 2 G920187 Supplement 1	Submission to FDA	Follow-up to 1/22/93 telephone call with FDA
1/29/93	PMA and All IDE's	Telephone Call with FDA	Discussion regarding change to packaging specifications as requested in 1/6/92 submission to FDA
2/5/93	PMA and All IDE's	Letter from FDA	Conditional approval of protocol 13192 and request for additional information, and approval of change to packaging specifications as requested in 1/6/93 submission to FDA
2/11/93	PMA P900059	Telephone Call with FDA	Discussion regarding post-market approval clinical study protocols
2/12/93	IDE G870144 Supplement 52 IDE G920008 Supplement 3 G920187 Supplement 5	Submission to FDA	Progress Report and proposed change to specifications for product usage

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2/22/93	IDE G920187 Amendment 1	Telephone Call with FDA	Discussion regarding 2/5/93 letter from FDA
2/25/93	PMA and All IDE's	Letter from FDA	Follow-up to 1/28/93 submission to FDA and request for additional information
3/3/93	PMA and All IDE's	Telephone Call with FDA	Discussion regarding 1/28/93 submission from FDA and 2/25/93 letter from FDA
3/5/93	PMA and All IDE's	Telephone Call with FDA	Discussion regarding post-market approval clinical studies and 2/12/93 submission to FDA
3/9/93	PMA P900059	Telephone Call with FDA	Request for meeting with FDA to discuss post-market approval clinical studies
3/10/93	PMA P900059	FAX to FDA	Agenda for upcoming meeting at FDA
3/10/93	IDE G920187 Supplement 2	Submission to FDA	Request for extension of time to respond to 2/5/93 letter from FDA
3/18/93	PMA and All IDE's	Telephone Call with FDA	Request for status regarding 2/12/93 submission to FDA
3/18/93	PMA and All IDE's	Letter from FDA	Conditional approval of proposed change to specifications for product usage as requested in 2/12/93 submission to FDA and request for additional information
3/26/93	PMA P900059	FAX to FDA	Revised list of attendees for upcoming meeting with FDA
3/29/93	PMA and All IDE's	Meeting with FDA	Discussion regarding 2/12/93 submission to FDA and post-market approval clinical study protocols
4/7/93	PMA P900059	Telephone Call with FDA	Discussion regarding post-market approval clinical study protocols and follow-up to 3/29/93 meeting with FDA
4/15/93	IDE G920187 Supplement 2	Letter from FDA	Approval of request for extension of time to respond to 2/5/93 letter from FDA
4/15/93	PMA and All IDE's	Telephone Call with FDA	Discussion regarding post-market approval clinical studies and 2/5/93 letter from FDA
4/16/93	PMA P900059	Telephone Call with FDA	Discussion regarding post-market approval clinical study protocols
4/16/93	PMA P900059	Telephone Call with FDA	Discussion regarding Summary of Safety and Effectiveness
4/21/93	PMA P900059	Telephone Call with FDA	Discussion regarding post-market approval clinical study protocol
4/26/93	IDE G870144 Supplement 53 IDE G920187 Supplement 6 G920008 Supplement 4	Submission to FDA	Response to 2/25/93 letter from FDA
4/28/93	PMA P900059 Amendment 15	Submission to FDA	Summary of Safety and Effectiveness, information regarding post-market approval clinical study protocols and further response to 2/25/93 letter from FDA
5/4/93	PMA P900059 Amendment 16	Submission to FDA	Progress Report

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5/10/93	PMA P900059 G920187	IDE Telephone Call with FDA	Discussion regarding Protocol 13192 and request for status of PMA
5/17/93	PMA P900059 Amendment 15 & 16	Telephone Call with FDA	Request for confirmation of receipt of 4/28/93 and 5/4/93 submissions to FDA
5/19/93	IDE G870144 Supplement 54	Submission to FDA	Amendment to protocol 13391
5/21/93	IDE G920187 Supplement 3	Submission to FDA	Response to 2/5/93 letter from FDA regarding Protocol 13192
5/26/93	IDE G930102 Original	Submission to FDA	Addition of Protocol A-1000
5/27/93	PMA and All IDE's	Letter from FDA	Conditional approval of change to specifications for product usage as requested in 2/12/93 submission to FDA and request for additional information
5/28/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
6/2/93	IDE G920187	Letter from FDA	Conditional approval of Protocol 13192 and request for additional information
6/8/93	IDE G930102	Letter from FDA	Acknowledgment of receipt of Protocol A-1000 and assignment of IDE number
6/8/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
6/14/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
6/16/93	IDE G920008 Supplement 5 G930102 Supplement 1 G870144 Supplement 55 IDE G920187 Supplement 7	IDE IDE Submission to FDA	Additional information regarding change to specification for product usage as request in 5/27/93 letter from FDA
6/17/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
6/18/93	IDE G870144 Supplement 54	Letter from FDA	Conditional approval of Protocol 13391 as amended 5/19/93 and request for additional information
6/23/93	IDE G920187	Letter from FDA	Approval of Protocol 13192 as amended 1/6/93
6/25/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
6/25/93	IDE G930102	Letter from FDA	Conditional approval of Protocol A-1000 and request for additional information
6/28/93	IDE G870144	Letter to FDA	Request for permit to export to Canada
7/2/93	IDE G920187 Supplement 4	Submission to FDA	Additional information regarding Protocol 13192
7/6/93	PMA P900059	Telephone Call with FDA	Request for Status of PMA
7/8/93	PMA P900059	Telephone Call with FDA	Request for status of permit to export to Japan
7/9/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
7/12/93	IDE G930102	Telephone Call with FDA	Request for status of Protocol A-1000
7/12/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
7/16/93	PMA and All IDE's	Letter from FDA	Approval of change to specifications for product usage as requested in 2/12/93 submission to FDA
7/19/93	PMA P900059	Telephone Call with FDA	Request for status of permit to export to Japan

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7/23/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
7/28/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
7/30/93	IDE G870144	Letter from FDA	Approval of request for permit to export to Canada
8/5/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
8/5/93	IDE G930102 Supplement 2	Submission to FDA	Response to 6/25/93 letter from FDA
8/5/93	IDE G920187	Letter from FDA	Acknowledgement of receipt of internal review board approval for Protocol 13192 and notification of requirement to make change to informed consent document
8/6/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
8/10/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
8/10/93	IDE G870144 Supplement 56	Submission to FDA	Second amendment to Protocol 13391 in response to 6/18/93 letter from FDA
8/13/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
8/16/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
8/20/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
8/30/93	PMA and All IDE's	Telephone Call with FDA	Discussion regarding clinical information
9/3/93	PMA P900059 Amendment 17	Submission to FDA	Notification of legal representative
9/3/93	IDE G930102	Letter from FDA	Approval of Protocol A-1000
9/8/93	PMA P900059	Telephone Call with FDA	Discussion regarding product manufacturing
9/10/93	IDE G870144	Letter from FDA	Approval of Protocol 13391 as amended 8/10/93
9/14/93	IDE G930102 Supplement 3	Submission to FDA	Additional information regarding Protocol A-1000
9/15/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
9/20/93	IDE G870144 Supplement 57	Submission to FDA	Progress Report
9/22/93	PMA P900059	Telephone Call with FDA	Discussion regarding product specifications
9/23/93	PMA and All IDE's	Letter from FDA	Follow-up to 8/30/93 telephone call with FDA
9/30/93	IDE G870144	Letter to FDA	Request for status of permit to export to Japan
10/4/93	IDE G870144	Letter from FDA	Approval of request for permit to export to Japan
10/11/93	IDE G870144 Supplement 58 IDE G920187 Supplement 8 IDE G920008 Supplement 6	Submission to FDA	Follow-up to 9/23/93 letter from FDA
10/15/93	IDE G930102 Supplement 3	Letter from FDA	Acknowledgement of receipt of 9/14/93 submission to FDA
10/19/93	IDE G870144	Telephone Call with FDA	Discussion regarding export to Canada
10/21/93	IDE G870144	Letter from FDA	Acknowledgement of receipt of Progress Report dated 9/20/93
10/26/93	IDE G920187 Supplement 9	Submission to FDA	Progress Report
11/4/93	PMA P900059	Telephone Call with FDA	Discussion regarding packaging specifications

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11/12/93	PMA and All IDE's	Telephone Call with FDA	Discussion regarding clinical information
	IDE G870144 Supplement 59 IDE G920187 Supplement 9 IDE G920008 Supplement 7 IDE G930102		
11/12/93	Supplement 4	Submission to FDA	Follow-up to 11/12/93 telephone call with FDA
	IDE G870144 Supplement 60 IDE G920187 Supplement 10 IDE G920008 Supplement 8 IDE G930102		
11/18/93	Supplement 5	Submission to FDA	Update of investigator lists
11/19/93	PMA P900059	Telephone Call with FDA	Discussion regarding 11/12/93 submissions to FDA
11/22/93	IDE G930102 Supplement 6	Submission to FDA	Additional information regarding Protocol A-1000
11/24/93	IDE G920187	Letter from FDA	Acknowledgement of receipt of Progress Report dated 10/26/93 and request for additional information regarding Protocol 13192
11/30/93	PMA P900059	Telephone Call with FDA	Request for status of PMA and discussion regarding 11/12/93 submissions to FDA
12/6/93	PMA P900059	Fax to FDA	Request to schedule meeting with FDA
12/6/93	PMA P900059	Telephone Call with FDA	Request for status of PMA and discussion regarding meeting with FDA
12/6/93	IDE G920187 Supplement 12	Submission to FDA	Request to add study site to Protocol 13192
12/7/93	IDE G920187 Supplement 13	Submission to FDA	Correction to 12/6/93 submission to FDA
12/8/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
12/8/93	PMA P900059	Letter from FDA	Request for additional information
12/8/93	IDE G920187 Supplement 14	Submission to FDA	Request to add investigator to Protocol 13192
12/12/93	PMA P900059	Telephone Call with FDA	Request for status of PMA
12/14/93	PMA P900059	Fax to FDA	Request for telephone call with FDA
12/16/93	IDE G870144 Supplement 59 IDE G920187 Supplement 9 IDE G920008 Supplement 7 IDE G930102 Supplement 4	Letter from FDA	Request for additional information regarding 11/12/93 submissions to FDA

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12/22/93	IDE G920187 Supplements 12 & 14	Letter from FDA	Approval to add study site and investigator as requested in 12/6/93 and 12/8/93 submissions to FDA
12/23/93	IDE G930102 Supplement 6	Letter from FDA	Acknowledgement of receipt of 11/22/93 submission to FDA
12/24/93	PMA P900059 Amendment 18	Submission to FDA	Response to 12/8/93 letter from FDA
1/3/94	PMA P900059	Telephone Call with FDA	Discussion regarding 12/24/93 submission to FDA
1/4/94	PMA P900059	Telephone Call with FDA	Discussion regarding status of PMA
1/5/94	PMA P900059	Fax to FDA	Request for telephone call with FDA to discuss status of PMA
1/6/94	IDE G920187 Supplement 15	Submission to FDA	Response to 11/24/93 letter from FDA
1/13/94	PMA P900059 Amendment 19	Submission to FDA	Correction to 12/24/93 submission to FDA
1/14/94	PMA P900059	Telephone Call with FDA	Discussion regarding 12/16/93 submission to FDA
1/21/94	PMA P900059	Telephone Call with FDA	Discussion regarding 12/16/93 submission to FDA
1/24/94	IDE G920008 Supplement 9	Submission to FDA	Progress Report
1/26/94	PMA P900059 Amendment 20	Submission to FDA	Additional response to 12/8/93 letter from FDA
2/2/94	PMA P900059	Telephone Call with FDA	Request for status of PMA
2/3/94	PMA P900059	Fax to FDA	Request for status of PMA
2/4/94	IDE G920187	Letter from FDA	Acknowledgement of receipt of 1/6/94 submission to FDA
2/4/94	IDE G870144 Supplement 61 IDE G920187 Supplement 11 IDE G920008 Supplement 9 G930102 Supplement 6	Submission to FDA	Request for extension of time to respond to 12/16/93 letter from FDA
2/22/94	IDE G870144 Supplement 62 IDE G920187 Supplement 12 IDE G920008 Supplement 10 IDE G930102 Supplement 7	Submission to FDA	Response to 12/16/93 letter from FDA
2/24/94	IDE G920008	Letter from FDA	Acknowledgement of receipt of Progress Report dated 1/24/94
3/25/94	PMA P900059	Telephone Call with FDA	Discussion regarding status of PMA
3/25/94	PMA P900059	Fax to FDA	Follow-up to 3/25/93 telephone call with FDA
3/28/94	PMA P900059	Telephone Call from FDA	Request for status of PMA

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3/28/94	PMA P900059	Fax to FDA	Request for telephone call with FDA to discuss status of PMA
3/29/94	PMA P900059	Telephone Call with FDA	Discussion regarding status of PMA
3/29/94	PMA P900059	Fax to FDA	Follow-up to 3/25/94, 3/28/94 and 3/29/94 telephone calls with FDA
3/30/94	PMA P900059	Fax to FDA	Additional follow-up to 3/28/94 telephone call with FDA
3/31/94	IDE G870144 Supplement 62 IDE G920187 Supplement 12 IDE G920008 Supplement 10 IDE G930102 Supplement 7	Letter from FDA	Acceptance of 2/22/94 submissions to FDA
4/4/94	PMA P900059 Amendment 21	Submission to FDA	Information regarding marketing and clinical studies
4/15/94	IDE G940051 Original	Submission to FDA	Addition of protocol A-3000.
4/19/94	IDE G940051	Letter from FDA	Acknowledgement of receipt of Protocol A-3000
4/26/94	PMA P900059	Letter from FDA	Notification that PMA is approvable and request for additional information
5/4/94	PMA P900059 Amendment 22	Submission to FDA	Response to 4/26/94 letter from FDA
5/18/94	IDE G9400051	Letter from FDA	Request for additional information regarding Protocol A-3000
5/31/94	PMA P900059 Supplement 22	Telephone Call with FDA	Discussion regarding 5/4/94 submission to FDA
6/1/94	PMA P900059 Supplement 22	Telephone Call from FDA	Discussion regarding 5/4/94 submission to FDA
6/2/94	PMA P900059 Supplement 22	Fax to FDA	Follow-up to 5/31/94 and 6/1/94 telephone calls with FDA
6/6/94	PMA P900059 Amendment 23	Submission to FDA	Additional follow-up to 5/31/94 and 6/1/94 telephone calls with FDA
7/15/94	IDE G940051 Amendment 1	Submission to FDA	Response to 5/18/94 letter from FDA
7/20/94	IDE G870144 Supplement 63	Submission to FDA	Progress Report
7/20/94	IDE G920008 Supplement 12	Submission to FDA	Final Report for Protocol 13491
8/5/94	PMA P900059	Notification from FDA	FDA APPROVAL OF PMA

# APPENDIX E

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: U.S. Patent 4,844,882

Issued: July 4, 1989

To: Widder et al.

For: CONCENTRATED STABILIZED  
MICROBUBBLE-TYPE ULTRASONIC  
IMAGING AGENT

DECLARATION

The Honorable Commissioner of Patents  
and Trademarks  
Box Patent Extension  
Washington, D.C. 20231

Sir:

The undersigned, attorney for Molecular Biosystems, Inc. in connection with the application for patent term extension, which is the Applicant for Extension of Patent Term under 35 USC §156 with regard to U.S. Patent No. 4,844,882, hereby declares that:

1. I am an attorney authorized to practice before the United States Patent and Trademark Office and have general authority to act on behalf of the owner in connection with the application for patent term extension of U.S. Patent No. 4,844,882.
2. I have reviewed and understand the contents of the application being submitted pursuant to 35 USC §156 and 37 CFR §1.740.
3. I believe the patent is subject to extension pursuant to 35 USC §156 and 37 CFR §1.710;
4. I believe an extension of the length claimed is justified under 35 USC §156 and the applicable regulations.
5. I believe the patent for which the extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 CFR §1.720.
6. I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any extension of patent term issuing thereon.

September 21, 1994.  
Date

Freddie K. Park  
Freddie K. Park, Reg. No. 35,636